

DOCKET NO.: ISIS-3013



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PATENT

REMARKS

Claims 27-29, and 33-34 are pending in this patent application. Claims 31 and 32 are canceled herein, without prejudice. Claim 29 is amended to depend from new claim 34 so as to provide an antecedent basis for the term "heteroatomic backbone modification." Claim 33 is amended to depend from a pending claim. No new matter has been added. Attached hereto is a marked-up version of the changes made to the claims by the present amendment. The attached page is captioned "Version with markings to show changes made."

Claim 31 has been canceled, without prejudice, thus rendering the objection of the Office Action moot. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 27, 28, and 31-33 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 34 of copending Application no. 08/847,151. Also, claim 29 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 34 of copending Application no. 08/847,151 in view of Milligan, Journal of Medicinal Chemistry, July 1993, Vol. 36, No. 14, pp. 1923-37) ("the Milligan reference"). Due to the provisional nature of the rejections, Applicants will address the same when there is an indication of otherwise allowable subject matter in the present application.

Applicants reiterate that due to the provisional nature of the rejection, it will be addressed upon the indication of allowable subject matter in the present application.

Rejections under 35 U.S.C. § 102

Claims 27, 28, 31 and 32 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Agrawal *et al.*, *Biochem. Pharm.* 50 (4), pp. 571-576 (1995) ("the Agrawal reference"). Applicants do not concur. However, solely for purposes of advancing prosecution, Applicants have amended the claims to recite a method of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide comprising a 2'-O-alkoxyalkoxy modification, wherein said oligonucleotide hybridizes to said target nucleic acid, and modulates the expression thereof. Accordingly, the rejection has been rendered moot by amendment, as the claims no longer recite "2'-O-alkyl modification". Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 27, 28, 31 and 32 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,005,094 to Simon *et al.* ("the Simon patent"), or in the alternative, by U. S. Patent No. 5,792,615 to Arnold Jr, *et al.* ("the Arnold patent"). Applicants do not concur. As discussed above, the rejection has been obviated by amendment. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Claims 27-19 and 31-33 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over any one of the Simon patent, the Arnold patent, and the Agrawal reference, taken separately and each further in view of Hanecak *et al.*, "Antisense Oligonucleotide Inhibition of Hepatitis C Virus Gene Expression in Transformed Hepatocytes", *J. of Virology*, 1996, pp. 5203-12

("the Hanecak reference"), Vlassov *et al.*, "Penetration of Oligonucleotides into Mouse Organism Through Mucosa and Skin", FEBS Letters 327 (3), 1993, pp. 271-74 ("the Vlassov reference"); and Milligan *et al.*, J. of Medicinal Chemistry, July 1993, Vol. 36, No. 14, pp. 1923-37 ("the Milligan reference"). Applicants do not concur.

As acknowledged by the Examiner on page 9 of the Office Action, none of the Simon and Arnold patents or the Agrawal reference, discloses or suggests oligonucleotides comprising a 2'-alkoxyalkoxy modification (e.g., 2'-methoxyethoxy modification or methylene(methylimino)) as recited in the present claims. None of the cited references, even when combined, would produce a claimed invention. Accordingly, the Simon patent, the Arnold patent and the Agrawal reference taken separately do not render the claims unpatentable.

With respect to the cited references taken in view of the Hanecak, Vlassov and Milligan references, Applicants submit that one of ordinary skill in the art would not have been motivated to modify the teachings of the Simon patent, the Arnold patent or the Agrawal reference in view of any of the Hanecak, Vlassov or Milligan references to produce a claimed invention.

"A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." In re Kotzab, 217 F.3d 1365, 1369, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (quoting *Interconnect Planning Corp. v. Feil*, 774 F. 2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985).

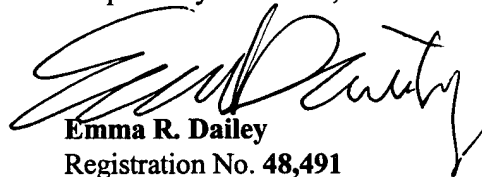
To establish a *prima facie* case of obviousness, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant."

In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). "In other words, the examiner must show reasons that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998).

Applicants submit that absent the disclosure in the present patent application, those of ordinary skill in the art would not have been motivated to modify the teachings of the Simon and Arnold patents or the Agrawal reference to produce a claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

In view of the foregoing, Applicants submit that the claims presently before the Examiner are in condition for allowance. An Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,


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Date: **January 22, 2002**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please cancel claims 31 and 32, without prejudice, and add claim 34. Please amend claims 27, 29 and 33 as presented below:

27. (Amended) A method of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide comprising a [2'-O-alkyl or] 2'-O-alkoxyalkoxy modification, wherein said oligonucleotide hybridizes to said target nucleic acid, and modulates the expression thereof.

29. (Amended) The method of claim [27] 34 wherein said heteroatomic backbone modification is a methylene(methylimino) modification.

33. (Amended) The method of claim [31] 27 wherein said 2'-alkoxyalkoxy modification is a 2'-methoxyethoxy modification.